Communication

A Short and Highly Stereoselective Synthesis of Cerebrosterol†

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The title compound, cerebrosterol, has been synthesized in five steps with 61.5% overall yield and >99.9% *de* from 3α, 6α-dimethoxymethoxyl-5β-cholane-24-al as a key intermediate, which was prepared from methyl 3α,6α-dihydroxy hyodeoxycholanate

Keywords cerebrosterol, methyl 3α,6α-dihydroxy hyodeoxycholanate, diisopropylzinc, stereoselective synthesis

Cerebrosterol (24*S*-hydroxycholesterol, **1**) formed in small amounts in human and animal brain[1] from cholesterol is important for cholesterol homeostasis in this organ. The excess cholesterol is converted into 24*S*-hydroxycholesterol by a unique brain-specific 24*S*-hydroxylase, which could be readily secreted from the central nervous system into the plasma and be taken up by the liver and further metabolized.[2] Alzheimer's disease (AD) and vascular demented patients appear to have higher circulating levels of cerebrosterol. It is speculated that cerebrosterol may potentially be used as a peripheral indicator of neuronal degeneration and potential state marker for AD.[3] Moreover, cerebrosterol can significantly activate LXRα and LXRβ, two orphan members of the nuclear receptor superfamily, and play a critical role in the regulation of cholesterol homeostasis. The activated LXRs form a permissive heterodimer with the 9-*cis*-retinoic acid receptor RXR and then regulate the transcriptional expression of their target genes, such as CYP7A,[4] SREBP-1c5,[5] ABCB1,[6a,6b] ABCG1,[6c] ABCG5/ABCG8,[6d] ApoE,[7] CETP,[8] LPL[9], *etc*. Thus, the cerebrosterol may be a potential drug for treatment for atherosclerosis.

The early synthesis of cerebrosterol relied on resolution via either recrystallization or chromatography of a mixture of 24*R*- and 24*S*-hydroxycholesterol benzoate.[10] Recently, several examples were reported of the stereoselective introduction of 24*S*-hydroxy group into the side chain of cholesterol.[11] Most of them took long steps to construct the side chain of cerebrosterol by using stigmasterol[11a,11b] as starting material, or cholest-25-en-24-one[11c] and desmosterol[11e,11f] as the intermediates. Although in 1995, Okamoto *et al*.[11d] utilized steroidal 3-silylated 24-aldehyde obtained from 3β-hydroxy-Δ^5-cholenic acid to react with diisopropylzinc using (1*R*,2*S*)-(+)2-(*N*,*N*-di-*n*-butylamino)-1-phenylpropan-1-ol [(+)-DBNE] as a chiral ligand to give 3β-acetoxy cerebrosterol in 63% yield with 87% *de*, the result is not very satisfactory. Furthermore, to prepare 24-aldehyde from 3β-hydroxy-Δ^5-cholenic acid, which was obtained from 3β-hydroxy-Δ^5-pregnene-20-one, required lots of steps.[12] Since methyl hyodeoxycholanate (Me-HDCA, **2**) is very cheap and readily available in China and can be efficiently converted to steroidal 3α, 6α-bismethoxylmethyl ether 24-aldehyde (**3**),[11f] it is used to directly construct the side chain of cerebrosterol via the asymmetric isopropylation of **3**. Moreover, the two retained alkoxyl groups at the C-3 and C-6 positions in steroidal 24-aldehyde **3** may facilitate the addition of diisopropylzinc because it was reported that 1α,3β-bisilylated cholenic aldehyde reacted with diisopropylzinc catalyzed by chiral β-amino alcohol ligand (+)-DBNE to afford the isopropylated adduct in a much higher yield than 3β-silylated cholenic aldehyde.[11d] More-

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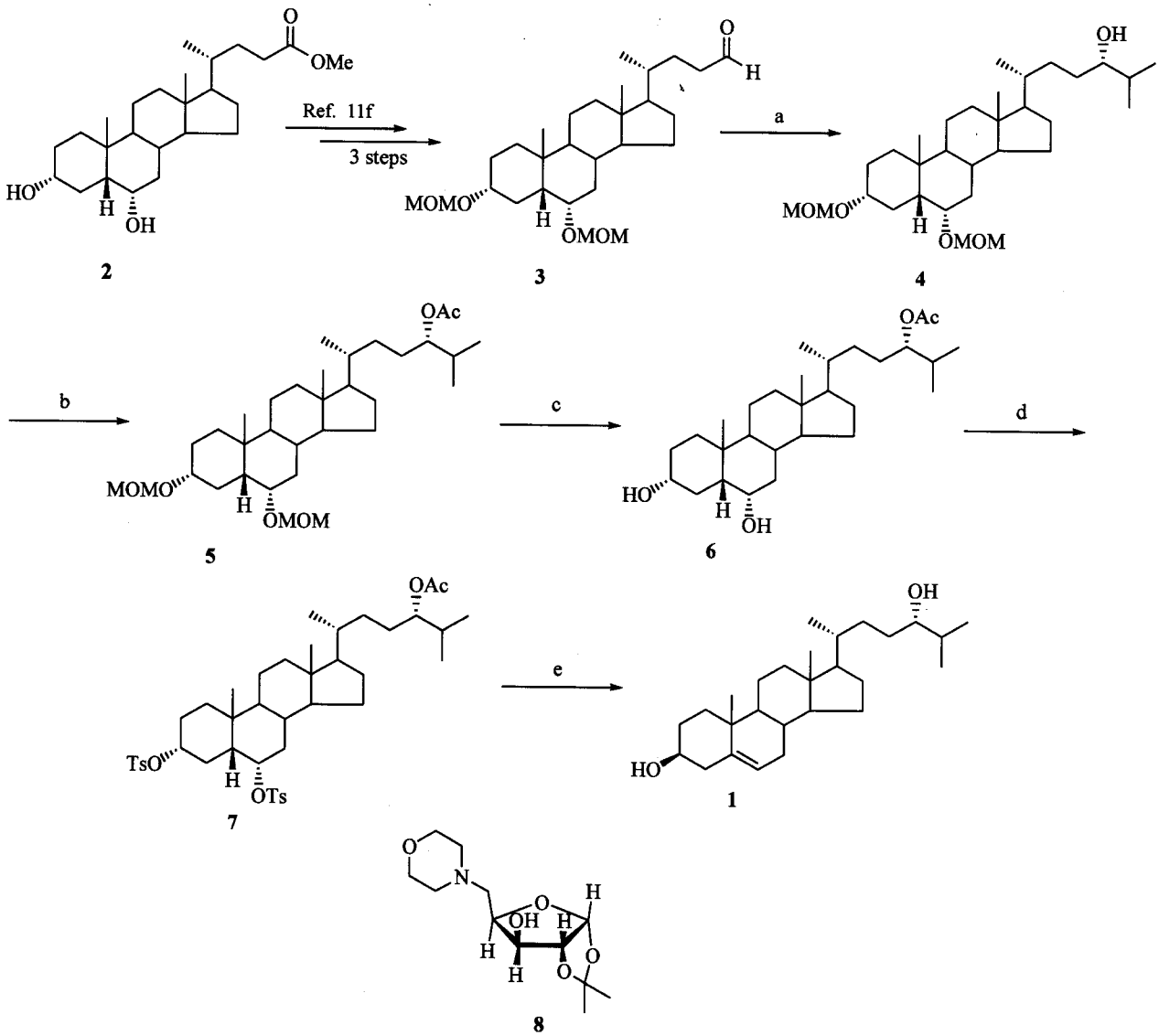
over, the 3α, 6α-bismethoxylmethyl ether group in the steroidal 24-aldehyd **3** can be easily converted to the Δ^5-3β-ol moiety[13] after it is isopropylated. So we select Me-HDCA as the starting material to synthesize cerebrosterol (**1**).

The practically synthetic route to cerebrosterol is outlined in Scheme 1. The key intermediate, steroidal 3α, 6α-bismethoxylmethyl ether 24-aldehyde (**3**), was prepared efficiently from Me-HDCA in 85.5% overall yield for three steps according to our previous work.[11f] With the steroidal aldehyde **3** in hand, our attention was turned to asymmetric isopropylation of the steroidal 24-aldehyde. Very recently, Yang and Cho[14] reported that the enantionselective addition of diisopropylzinc to alkyl and aryl aldehyde catalyzed by a γ-dialkylamino alcohol, 1, 2-*O*-isopropylidene-5-deoxy-5-morprolino-α-*D*-xylofutanose (**8**), which is easily available from α-*D*-xyloxe, with very high enantiomeric excess and yield. We applied this novel ligand for the asymmetric addition of the steroidal aldehyde **3** with diisopropylzinc. Thus **3** was isopropylated with 20 mol% chiral ligand **8** in toluene at 0 ℃ for 4 h. As expected, the reaction proceeded smoothly

Scheme 1



Reagents and conditions: a) $^i Pr_2Zn$, ligand **8**, toluene, 0 ℃, 85%, *de* > 99.9%; b) Ac_2O, Py, 99%; c) PPTs, ^{t}BuOH, reflux, 88%; d) TsCl, Py, quant.; e) KOAc, DMF, reflux, then KOH, MeOH, reflux, 83%.

to provide the 24*S*-hydroxy product in 85% yield and >99.9% *de*[15] The high yield and *de* may be owing to the special structure of steroidal aldehyde **3** or the novel ligand or both. Acetylation of **4** with acetic anhydride in the presence of pyridine gave the acetate **5** in 99% yield, then removal of 3α,6α-dihydroxy protective groups by refluxing with PPTS in ^{t}BuOH afforded the 3α,6α-dihydroxy cholesterol (**6**) in 88% yield. Ditosylation of **6** with *p*-toluene sulfonyl chloride in pyridine at 0 ℃ provided quantitatively the ditosylate **7** which was treated with potassium acetate in DMF-water at 105 ℃[13] followed by hydrolysis of the ester with potassium hydroxide in methanol to give the target molecule cerebrosterol (**1**) in 83% yield.[16]

The advantages of this synthesis of cerebrosterol are the easy availability of starting material (Me-HDCA) and a short route with high diastereoselectivity (>99.9% *de*).

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15 (a) Compound **4**: $[\alpha]_D^{20}$ + 4.8 (*c* 0.965, $CHCl_3$); MS (70 eV) *m/z* (%): 444 (8.9), 384 (53.8), 45 (100.0); IR (KBr) ν: 3503 (OH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.64 (s, 3H, 18-CH_3), 0.89 (d, J = 6.8 Hz, 3H, 21-CH_3), 0.911—0.920 (m, 6H, 19-CH_3, 26-CH_3), 0.94 (d, 3H, J = 2.1 Hz, 27-CH_3), 3.30—3.36 (m, 1H, 24-H), 3.37 (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3), 3.45—3.59 (m, 1H, 3β-H), 3.90—3.94 (m, 1H, 6β-H), 4.65—4.74(m, 4H, $OCH_2O \times 2$). Anal. calcd for $C_{31}H_{56}O_5$: C 73.18, H 11.09; found C 73.02, H 10.77. The diastereoselective ratio of the product was determined by HPLC analysis on Inersil ODS column (4.6 × 250 mm) with CH_3CN as eluent. The absolute configuration was identified by comparasion with authentic sample.[15b]
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16 Compound **1**: yield 83%; m.p. 173—174 ℃ (lit.[10a] m.p. 175—176 ℃; lit.[17] m.p. 181—182.5 ℃); $[\alpha]_D^{20}$ − 48 (*c* 0.245, $CHCl_3$) (lit.[17] $[\alpha]_D$ − 48.3, $CHCl_3$); MS (70 eV) *m/z* (%): 402 (52.4), 384 (38.8), 369 (18.0), 351 (14.7); IR (KBr) ν: 3370 (OH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.68 (s, 3H, 18-CH_3), 0.89 (d, J = 6.8 Hz, 3H, 21-CH_3), 1.01 (s, 3H, 19-CH_3), 3.28—3.35 (m, 1H, 24-H), 3.47—3.58 (m, 1H, 3α-H), 5.35 (d, J = 4.8 Hz, 1H, 6-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 140.8 (5-C), 121.8 (6-C), 77.5 (24*S*-C), 77.3 (24*R*-C), 71.9 (3-C), 56.8 (14-C), 56.0 (17-C), 50.2 (9-C), 42.5 (13-C), 42.4 (4-C), 39.9 (12-C), 37.3 (1-C), 36.6 (10-C), 36.0 (20-C), 33.2 (25-C), 32.3 (22-C), 32.1 (2-C), 32.0 (8-C), 31.7 (7-C), 30.8 (23-C), 28.3 (16-C), 24.3 (15-C), 21.2 (11-C), 19.5 (19-C), 19.1 (21-C), 18.9 (17-C), 16.8 (26-C), 12.0 (18-C). HREIMS calcd for $C_{27}H_{46}O_2[M^+]$, 402.3498, found 402.3533.

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